☐1: NP_032013. tumor necrosis fa...[gi:6679751]

BLink, Domains, Nucleotide, OMIM, Related Sequences, Domain Relatives, PubMed, Taxonomy, LinkOut

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LOCUS       Tnfrsf6                   327 aa            linear   ROD 18-AUG-2002
DEFINITION  tumor necrosis factor receptor superfamily, member 6; Fas antigen;
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ACCESSION   NP_032013
VERSION     NP_032013.1  GI:6679751
DBSOURCE    REFSEQ: accession NM_007987.1
KEYWORDS    .
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REFERENCE   1  (residues 1 to 327)
  AUTHORS   Watanabe-Fukunaga,R., Brannan,C.I., Itoh,N., Yonehara,S.,
            Copeland,N.G., Jenkins,N.A. and Nagata,S.
  TITLE     The cDNA structure, expression, and chromosomal assignment of the
            mouse Fas antigen
  JOURNAL   J. Immunol. 148 (4), 1274-1279 (1992)
  MEDLINE   92148151
   PUBMED   1371136
REFERENCE   2  (residues 1 to 327)
  AUTHORS   Adachi,M., Watanabe-Fukunaga,R. and Nagata,S.
  TITLE     Aberrant transcription caused by the insertion of an early
            transposable element in an intron of the Fas antigen gene of lpr
            mice
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 90 (5), 1756-1760 (1993)
  MEDLINE   93189576
   PUBMED   7680478
REFERENCE   3  (residues 1 to 327)
  AUTHORS   Chu,J.L., Drappa,J., Parnassa,A. and Elkon,K.B.
  TITLE     The defect in Fas mRNA expression in MRL/lpr mice is associated
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  JOURNAL   J. Exp. Med. 178 (2), 723-730 (1993)
  MEDLINE   93340650
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  AUTHORS   Carninci,P. and Hayashizaki,Y.
  TITLE     High-efficiency full-length cDNA cloning
  JOURNAL   Meth. Enzymol. 303, 19-44 (1999)
  MEDLINE   99279253
   PUBMED   10349636
REFERENCE   5  (residues 1 to 327)
  AUTHORS   Carninci,P., Shibata,Y., Hayatsu,N., Sugahara,Y., Shibata,K.,
            Itoh,M., Konno,H., Okazaki,Y., Muramatsu,M. and Hayashizaki,Y.
  TITLE     Normalization and subtraction of cap-trapper-selected cDNAs to
            prepare full-length cDNA libraries for rapid discovery of new genes
  JOURNAL   Genome Res. 10 (10), 1617-1630 (2000)
  MEDLINE   20499374
   PUBMED   11042159
REFERENCE   6  (residues 1 to 327)
  AUTHORS   Shibata,K., Itoh,M., Aizawa,K., Nagaoka,S., Sasaki,N., Carninci,P.,
            Konno,H., Akiyama,J., Nishi,K., Kitsunai,T., Tashiro,H., Itoh,M.,
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            Sumi,N., Ishii,Y., Nakamura,S., Hazama,M., Nishine,T., Harada,A.,
            Yamamoto,R., Matsumoto,H., Sakaguchi,S., Ikegami,T., Kashiwagi,K.,
            Fujiwake,S., Inoue,K. and Togawa,Y.
  TITLE     RIKEN integrated sequence analysis (RISA) system--384-format
            sequencing pipeline with 384 multicapillary sequencer
  JOURNAL   Genome Res. 10 (11), 1757-1771 (2000)
  MEDLINE   20530913
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Revised: July 5, 2002.

*134637 Nucleotide, Related Entries, Protein, PubMed, LinkOut

TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 6; TNFRSF6

Alternative titles; symbols

APOPTOSIS ANTIGEN 1; APT1
FAS ANTIGEN
SURFACE ANTIGEN APO1; APO1
CD95

Gene map locus 10q24.1

TEXT

Cloning of Fas antigen cDNA from human (Itoh et al., 1991) and mouse cells indicated that the antigen is a protein containing a single transmembrane domain with a calculated molecular weight of 35,000. It shows structural homology with a number of cell-surface receptors, including tumor necrosis factor (TNF) receptors (191190, 191191) and low-affinity nerve growth factor receptor (162010). Northern analysis indicated that Fas antigen mRNA is expressed in a limited number of tissues, including thymus, liver, ovary, and heart. When human Fas antigen is expressed in mouse cell lines, it can induce antibody-triggered cell death. Characterization of the process indicated that Fas antigen mediates apoptosis, or programmed cell death.

Watanabe-Fukunaga et al. (1992) demonstrated that mice carrying the lymphoproliferation (lpr) mutation have defects in the Fas antigen gene. These mice develop lymphadenopathy and suffer from a systemic lupus erythematosus-like autoimmune disease (152700), indicating an important role for Fas antigen in the negative selection of autoreactive T cells in the thymus. The point mutation in the Fas gene in the lpr mouse was a T-to-A transversion causing the substitution of asparagine for isoleucine. Frizzera et al. (1989) identified human patients displaying a phenotype similar to that of lpr mice. Watanabe-Fukunaga et al. (1992) mapped the mouse Fas gene to the distal region of chromosome 19. Inazawa et al. (1992) mapped the human FAS gene to 10q24.1 by fluorescence in situ hybridization.

The APO1 antigen (48 kD) defined by the mouse monoclonal antibody anti-APO1 is expressed on the cell surface of various normal and malignant cells including activated human T and B lymphocytes and a variety of malignant human lymphoid cell lines. APT1 cDNA shows significant sequence similarity to members of the tumor necrosis factor/nerve growth factor receptor superfamily (Oehm et al., 1992) and is in fact the same as the Fas antigen. Binding of anti-APO1 antibody to the APO1 antigen induces apoptosis. Using cosmid DNA containing the APT1 gene as a probe for fluorescence in situ hybridization, Lichter et al. (1992) mapped the gene to a subregion of chromosomal band 10q23. The analysis showed that the

APT1 gene is located just distal to the central part of band 10q23.

Talal (1994) used the term autogene, a neologism, to refer to a gene whose abnormal function contributes to the development of autoimmune disease (parallel to the term oncogene and the role of its product in malignancy). Mountz and Talal (1993) suggested that FAS is the first known autogene. Wu et al. (1993) observed autoimmune disease in mice due to integration of endogenous retrovirus in the FAS gene.

Peripheral activated T cells (ATC) from 'lymphoproliferation' (lpr/lpr) mutant mice that express a reduced number of APO1 receptors have a defect in T-cell receptor (TCR)-induced apoptosis. Dhein et al. (1995) reported experiments suggesting that TCR-induced apoptosis in ATC occurs through an apo1 ligand-mediated autocrine suicide. Their results suggested a mechanism for suppression of the immune response and for peripheral tolerance by T-cell deletion. Brunner et al. (1995) provided supporting evidence by showing that the interaction between Fas and Fas ligand (134638) inhibits activation-induced apoptosis. Because T-cell receptor ligation can induce apoptosis in a single T hybridoma cell, Brunner et al. (1995) suggested that the Fas/Fas ligand interaction can induce cell death in a cell-autonomous manner. Ju et al. (1995) likewise showed that the interaction between Fas and Fas ligand accounts for activation-induced T-cell death.

Mannick et al. (1999) demonstrated that Fas activates caspase-3 (600636) not only by inducing the cleavage of the caspase zymogen to its active subunits but also by stimulating the denitrosylation of its active site thiol.

Viard et al. (1998) detected high levels of soluble Fas ligand in the sera of patients with toxic epidermal necrolysis (TEN). Keratinocytes of TEN patients produced Fas ligand, which induced keratinic apoptosis. Incubating keratinocytes with intravenous immunoglobulin (IVIG) completely inhibited Fas-mediated keratinocyte apoptosis. A naturally occurring anti-Fas immunoglobulin present in IVIG blocks the Fas receptor and mediates this response. Ten patients with TEN were treated with IVIG. Progression of skin disease was rapidly reversed in all cases.

Rieux-Laucat et al. (1995) analyzed expression of the FAS antigen and its function in 3 children (including 2 sibs) with a lymphoproliferative syndrome, 2 of whom also had autoimmune disorders. A large deletion in the FAS gene and no detectable cell surface expression characterized the most affected patient. Clinical manifestations in the 2 sibs were less severe: FAS-mediated apoptosis was impaired and a deletion within the intracytoplasmic domain was detected.

Fisher et al. (1995) described 5 unrelated children with a rare autoimmune lymphoproliferative syndrome (ALPS; 601859) characterized by massive nonmalignant lymphadenopathy, autoimmune phenomena, and expanded populations of TCR-CD3(+)CD4(-)CD8(-) lymphocytes. These findings, suggesting a genetic defect in the ability of T lymphocytes to respond to normal immunoregulatory mechanisms, prompted an evaluation of lymphocyte apoptosis. Each child had defective FAS-mediated T lymphocyte apoptosis associated with a unique, deleterious FAS gene mutation. One mutation appeared to cause a simple loss of function; however, 4 others had a dominant-negative phenotype when coexpressed with normal FAS. Thus, FAS is the cause of this disorder of lymphocyte homeostasis and peripheral self tolerance. One of the patients studied by Fisher et al. (1995) was included in the report by Sneller et al. (1992), delineating this disorder and pointing out its resemblance to lpr/gld disease in the mouse. (The lpr and gld mice bear mutated genes for CD95 and CD95 ligand (134638), respectively.) In both the mouse and the human, hypergammaglobulinemia is a prominent feature of the disease. In the mouse, autoantibodies, especially antinuclear antibodies, form immune complexes that are deposited in the kidney to cause glomerulonephritis. Autoantibodies were seen by Fisher et al. (1995) in only 2 of the ALPS patients, and antinuclear antibodies were not observed. However, one patient developed glomerulonephritis, and all 5

children had autoimmune cytopenias and rashes.

Simple recessive inheritance was ruled out by Fisher et al. (1995) in all 5 ALPS patients they studied because all showed 1 mutated FAS allele and 1 normal allele (see 134637.0001 through 134637.0005). This is in contrast to the mouse lpr mutations, which are recessive. In each case, the novel FAS mutation in the affected child was inherited from a carrier parent. Parental genetic mosaicism was observed in the mother of patient 4 (134637.0004) in whom a normal and a mutant FAS allele was observed with the same Alu type and whose apoptosis defect was less marked than that of her affected son. Fisher et al. (1995) referred to the dominant-negative mutations alternatively as dominant-interfering.

Fisher et al. (1995) suggested that modifier genes make a major contribution to the disease phenotype and account for the fact that the heterozygous parent was unaffected. In the mouse, the typical lpr autoimmune syndrome of glomerulonephritis, vasculitis, and arthritis is regularly manifested at an early age in the MRL mouse background, but by contrast, the same mutation causes essentially no autoimmune disease when bred onto the C57BL/6 background. On other backgrounds, such as C3H, the onset is delayed and the autoimmune manifestations are milder than in MRL mice. Thus, it is not surprising that in an outbred human population, individuals bearing the same FAS gene mutation may have dramatically different phenotypes. Defining the additional segregating gene(s) that causes expression of the full manifestations of ALPS in the presence of FAS dysfunction will be important for understanding how FAS participates in immune regulation. In ALPS patients, defects that might convert an asymptomatic FAS abnormality to overt disease are likely to be inherited from the parent who does not carry a FAS mutation. Elucidation of molecules involved in programmed death pathways suggests an abundance of potential candidate genes, including FASL, BCL2 (151430), and IL1B-convertase (147678). The father of patient 3 from whom the FAS mutation was inherited had died of Hodgkin disease and his brother, the uncle of patient 3, who also had Hodgkin disease, carried the FAS thr225-to-pro (134637.0003) mutation and showed defective apoptosis (Fisher et al., 1995).

Induction of apoptosis by oncogenes like MYC (190080) may be important in restraining the emergence of neoplasia. However, the mechanism by which MYC induces apoptosis had been unknown. Hueber et al. (1997) demonstrated that MYC-induced apoptosis requires interaction on the cell surface between CD95 and its ligand. The findings linked 2 apoptotic pathways previously thought to be independent and established the dependence of MYC on CD95 signaling for its killing activity.

Arscott et al. (1999) examined FAS expression in thyroid tissue derived from patients with papillary carcinoma and follicular cancer. More intense immunohistologic staining for the FAS protein was observed on papillary cancer cells as compared with adjacent normal follicles. FAS expression was detected at levels up to 3-fold higher in cancerous thyrocytes compared with paired normal cells. The authors concluded that the results demonstrate that the FAS antigen is expressed and functional on papillary thyroid cancer cells and that this may have potential therapeutic significance.

Hueber (2000) described the signaling pathway leading to apoptosis. CD95 crosslinking with CD95L (134638) results in the formation of a death-inducing signaling complex (DISC) composed of CD95, the signal adaptor protein FADD (602457), and procaspase 8. This association generates CASP8 (601763), activating a cascade of caspases. Lepple-Wienhues et al. (1999) showed that in addition to the role of CD95 in inducing cell death, stimulation of CD95 inhibits the influx of calcium normally induced by activation of the T-cell antigen receptor, in part by not affecting the release of calcium from intracellular stores. This block in calcium entry can be mimicked by stimulating T cells with acid sphingomyelinase metabolites of the plasma membrane lipid sphingomyelin, such as ceramide and sphingosine.

From their cohort of 11 families with ALPS, Vaishnaw et al. (1999) studied 8 patients to define the mechanisms responsible for defective CD95-mediated apoptosis. Mutations in and around the death domain of CD95 had a dominant-negative effect that was explained by interference with the recruitment of the signal adaptor protein FADD to the death domain. The intracellular domain (ICD) mutations were associated with a highly penetrant Canale-Smith syndrome phenotype (601859) and an autosomal dominant inheritance pattern. In contrast, mutations affecting the CD95 extracellular domain (ECD) resulted in failure of extracellular expression of the mutant protein or impaired binding to CD95 ligand. These mutations did not have a dominant-negative effect. In each of the families with an ECD mutation, only a single individual was affected. These observations were consistent with different mechanisms of action and modes of inheritance of ICD and ECD mutations, suggesting that individuals with an ECD mutation may require additional defect(s) for expression of Canale-Smith syndrome.

Jackson et al. (1999) found that of 17 unique APT1 mutations in unrelated ALPS probands, 12 (71%) occurred in exons 7 to 9, which encode the intracellular portion of FAS. In vitro, activated lymphocytes from all 17 patients showed apoptotic defects when exposed to an anti-FAS agonist monoclonal antibody. Similar defects were found in a FAS-negative cell line transfected with cDNAs bearing each of the mutations. In cotransfection experiments, FAS constructs with either intra- or extracellular mutations caused dominant inhibition of apoptosis mediated by wildtype FAS. Two missense FAS variants, not restricted to patients with ALPS, were identified. Variant A(-1)T (134637.0012) at the FAS signal sequence cleavage site, which mediates apoptosis less well than wildtype FAS and is partially inhibitory, was present in 13% of African American alleles. Among the ALPS-associated FAS mutants, dominant inhibition of apoptosis was much more pronounced in mutants affecting the intracellular, versus extracellular, portion of the FAS receptor. Mutations causing disruption of the intracellular FAS death domain also showed a higher penetrance of ALPS phenotype features in mutation-bearing relatives. Significant ALPS-related morbidity occurred in 44% of relatives with intracellular mutations, versus 0% of relatives with extracellular mutations. Thus, the location of mutations within APT1 strongly influences the development and the severity of ALPS.

Martin et al. (1999) contributed to the understanding of the mechanism by which heterozygous mutations in the CD95 receptor result in dominant interference with apoptosis leading to ALPS. They showed that local or global alterations in the structure of the cytoplasmic death domain from 9 independent ALPS CD95 death-domain mutations resulted in a failure to bind the FADD/MORT1 signaling protein. Despite heterozygosity for the abnormal allele, lymphocytes from ALPS patients showed markedly decreased FADD association and a loss of caspase recruitment and activation after CD95 crosslinking. These data suggested that intracytoplasmic CD95 mutations in ALPS impair apoptosis chiefly by disrupting death-domain interactions with the signaling protein FADD/MORT1.

Heterozygous mutations encoding abnormal forms of the death receptor Fas dominantly interfere with Fas-induced lymphocyte apoptosis in human ALPS. Siegel et al. (2000) found that this effect, rather than depending upon ligand-induced receptor oligomerization, stems from ligand-independent interaction of wildtype and mutant Fas receptors through a specific region of the extracellular domain. This domain, located within the first cysteine-rich domain, is termed the pre-ligand assembly domain (PLAD). Siegel et al. (2000) identified preassociated Fas complexes in living cells by means of fluorescence resonance energy transfer. In a large number of ALPS patients, they found that the PLAD was preserved in every example of dominant-negative mutation. To cause dominant interference, mutant protein must physically interact with wildtype protein in a preassociated receptor complex which normally permits Fas signaling.

Pestano et al. (1999) identified a differentiative pathway taken by CD8 cells bearing receptors that cannot engage class I MHC (see 142800) self-peptide molecules because of incorrect thymic selection, defects in peripheral MHC class I expression, or antigen presentation. In any of these cases, failed CD8 T-cell

receptor coengagement results in downregulation of genes that account for specialized cytolytic T-lymphocyte function and resistance to cell death (CD8-alpha/beta, see 186730; granzyme B, 123910; and LKLF, 602016), and upregulation of Fas and FasL death genes. Thus, MHC engagement is required to inhibit expression and delivery of a death program rather than to supply a putative trophic factor for T cell survival. Pestano et al. (1999) hypothesized that defects in delivery of the death signal to these cells underlie the explosive growth and accumulation of double-negative T cells in animals bearing Fas and FasL mutations, in patients that carry inherited mutations of these genes, and in about 25% of systemic lupus erythematosus patients that display the cellular signature of defects in this mechanism of quality control of CD8 cells.

Aspinall et al. (1999) identified 2 novel mutations in FAS that cause ALPS.

Using microdissection techniques to isolate tumor cells from biopsies of 21 burn scar-related squamous cell carcinomas, Lee et al. (1999) analyzed the entire FAS coding region and all of the splice sites and found somatic point mutations in 3 cases. No mutations were detected in 50 cases of conventional squamous cell carcinoma. The FAS mutations were located within the death domain (asn239 to asp; 134637.0014), ligand-binding domain (asn102 to ser; 134637.0015) and transmembrane domain (cys162 to arg; 134637.0016). Loss of heterozygosity (LOH) of the other FAS allele was demonstrated in tumors carrying the asn239-to-asp and cys162-to-arg mutations, and expression of Fas was confirmed in all tumors with Fas mutations. Burn scar-related squamous cell carcinomas are usually more aggressive than conventional squamous cell carcinomas, and Lee et al. (1999) suggested that somatic mutations in FAS may contribute to the development and/or progression of burn scar-related squamous cell carcinomas.

Grassme et al. (2000) showed that Pseudomonas aeruginosa infection induces apoptosis of lung epithelial cells by activation of the endogenous CD95/CD95L system. Deficiency of CD95 or CD95L on epithelial cells prevented apoptosis of lung epithelial cells in vivo as well as in vitro. The importance of CD95/CD95L-mediated lung epithelial cell apoptosis was demonstrated by the rapid development of sepsis in mice deficient in either CD95 or CD95L, but not in normal mice, after P. aeruginosa infection.

(Note on pronunciation: Beautyman (1995) stated that the word 'apoptosis' was 'taken straight from Liddell and Scott's classical Greek-English lexicon complete with examples of its use in medicine by Hippocrates and Dioscorides (the physician, not the poet).' He stated, furthermore, that for this reason it should be pronounced with 2 'p's. He pointed out that Kerr et al. (1972), in introducing the term into modern science, suggested silencing the second p. Silencing the p seems so well established in words of similar derivation, such as 'ptosis' and 'pneumonia,' that silencing of the second p would seem appropriate in modern speech.)

Natural inhibitors of angiogenesis are able to block pathologic neovascularization without harming the preexisting vasculature. Volpert et al. (2002) demonstrated that 2 such inhibitors, thrombospondin I (188060) and pigment epithelium-derived factor (172860), derive specificity for remodeling vessels from their dependence on Fas/Fas ligand-mediated apoptosis to block angiogenesis. Both inhibitors upregulated FasL on endothelial cells. Expression of the essential partner of FasL, Fas receptor, was low on quiescent endothelial cells and vessels but greatly enhanced by inducers of angiogenesis, thereby specifically sensitizing the stimulated cells to apoptosis by inhibitor-generated FasL. The antiangiogenic activity of thrombospondin I and pigment epithelium-derived factor both in vitro and in vivo was dependent on this dual induction of Fas and FasL and the resulting apoptosis. Volpert et al. (2002) concluded that this example of cooperation between pro- and antiangiogenic factors in the inhibition of angiogenesis provides one explanation for the ability of inhibitors to select remodeling capillaries for destruction.

ALLELIC VARIANTS

(selected examples)

.0001 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, 1-BP DEL, 429G]

In their patient 1 with ALPS1A (601859), Fisher et al. (1995) demonstrated heterozygosity for deletion of guanine-429 in exon 3 of the FAS gene, resulting in frameshift. The mother was heterozygous for the same mutation.

.0002 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, EX3DEL]

In their patient 2 with ALPS1A (601859), Fisher et al. (1995) found in-frame deletion of exon 3 of the FAS gene, resulting from an insertion in the 5-prime splice site of intron 3. The normal mother was heterozygous for the same mutation.

.0003 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, THR225PRO]

In their patient 3 with ALPS1A (601859), Fisher et al. (1995) found a A-to-C transversion of nucleotide 915 of the FAS gene, resulting in a thr225-to-pro substitution. The father had died of Hodgkin disease, but the paternal uncle, who also had Hodgkin disease, was found to be heterozygous for the same mutation as patient 3; thus, the father was the source of the mutation in patient 3.

.0004 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, IVS7AS, A-C, -2]

In their patient 4 with ALPS1A (601859), Fisher et al. (1995) identified an AG-to-CG change at the 3-prime splice site of intron 6 of the FAS gene, resulting in aberrant splicing. The mother was heterozygous for the same mutation, but appeared to be a mosaic.

.0005 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, GLN257TER]

In their patient 5 with ALPS1A (601859), Fisher et al. (1995) found a nonsense mutation of the FAS gene: a C-to-T transition of nucleotide 1011 resulted in conversion of the codon for gln257 to a stop codon. The mother had 1 normal FAS allele and 1 allele with the identical mutation found in the child.

.0006 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA, AUTOSOMAL RECESSIVE [TNFRSF6, ARG105TRP]

Bettinardi et al. (1997) described a family in which 3 sibs affected with ALPS1A (601859) were compound heterozygotes for missense mutations of the APT1 gene. The maternally-derived mutant allele carried a C-to-T transition at nucleotide 555, which resulted in an arg105-to-trp substitution of the FAS protein. The paternally-derived mutant allele carried an A-to-G transition at nucleotide 889, resulting in a tyr216-to-cys substitution (134637.0007). The children shared common features, including splenomegaly and lymphadenopathy, but only 1 developed severe autoimmune manifestations. No clinical or immunologic defect and no evidence of defective FAS function was identified in the parents, each of whom carried 1 of the 2 mutant alleles. The patient with autoimmune disease showed hemolytic anemia and thrombocytopenia. One of the others developed hypergammaglobulinemia, with increased IgG and IgA

serum levels.

.0007 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA, AUTOSOMAL RECESSIVE [TNFRSF6, TYR216CYS]

See 134637.0006 and Bettinardi et al. (1997).

.0008 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, ASP244VAL]

In a family with ALPS1A (601859) containing 11 affected individuals in 4 generations, Infante et al. (1998) found a 973A-T transversion in the Fas cDNA, predicted to cause a nonconservative substitution of valine for aspartic acid at position 244 in the intracellular domain of Fas. The family documented the autosomal dominant inheritance of the abnormality as well as the high degree of variability in clinical expression. Although 1 affected individual died of postsplenectomy sepsis and 1 had been treated for lymphoma, the FAS mutation in this family was compatible with a healthy adulthood, as clinical features of ALPS receded with increasing age.

.0009 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, ARG234PRO]

In their family P8 with a pedigree pattern consistent with autosomal dominant inheritance of ALPS1A (601859), Vaishnaw et al. (1999) demonstrated a CGA (arg)-to-CCA (pro) mutation in codon 234 of the CD95 gene. The mutation was located in the intracellular domain of the protein and had a dominant-negative effect. The family found to have the arg234-to-pro mutation by Vaishnaw et al. (1999) was originally reported by Rao et al. (1974) as an instance of splenomegaly with hypersplenism (183350).

.0010 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, THR254ILE]

In their family P9 with an autosomal dominant pedigree pattern of inheritance of ALPS1A (601859), Vaishnaw et al. (1999) found heterozygosity for an ACA (thr)-to-ATA (ile) mutation in codon 254 of the CD95 gene.

.0011 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, IVS7DS, T-A, +2]

In their family P10 with an autosomal dominant pattern of inheritance of ALPS1A (601859), Vaishnaw et al. (1999) found that the proband was heterozygous for a splice donor mutation in the CD95 gene, which resulted in frameshift and premature termination at position 209 (ser209 to ter).

.0012 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA [TNFRSF6, A-T, -1]

Jackson et al. (1999) found a variant A(-1)T at the FAS signal sequence cleavage site in 13% of African American TNFRSF6 alleles. The variant mediated apoptosis less well than wildtype FAS and was partially inhibitory.

.0013 AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME, TYPE IA, AUTOSOMAL RECESSIVE [TNFRSF6, IVS9, 20-BP DUP]

ALPS (601859) is usually inherited as an autosomal dominant; affected individuals are heterozygous for mutations in the FAS gene. Evidence for autosomal recessive inheritance was presented by van der Burg et al. (2000). They described a child with clinical features of ALPS without detectable FAS expression on freshly isolated blood leukocytes. Sequencing of the FAS gene revealed a 20-nucleotide duplication in the last exon affecting the cytoplasmic signaling domain. The patient was homozygous for this mutation, whereas the consanguineous parents and the sibs were heterozygous. The findings indicated that this phenotype was the human homolog of the FAS-null mouse, inasmuch as she carried a homozygous mutation in the FAS gene and showed severe and accelerated ALPS phenotype. The heterozygous family members did not have the ALPS phenotype, indicating that the disease-causing FAS mutation was autosomal recessive. Immediately after the birth of the girl reported by van der Burg et al. (2000), petechiae, generalized edema, and hepatosplenomegaly were noted. During the first month of life, autoantibodies against red blood cells and platelets were demonstrated. A liver biopsy showed extensive extramedullary hematopoiesis. Hypergammaglobulinemia persisted for several years. At the age of 8 months, she had massive generalized adenopathy of the cervical, mesenteric, and para-aortic lymph nodes, and chronic pulmonary disease did not respond to bronchodilation and was not associated with detectable pathogens. Cutaneous lupus-like disease appeared at a later stage. The patient showed histologically malignant lymph nodes, although monoclonal or oligoclonal rearrangements could not be detected on analysis of the gene encoding the T-cell antigen receptor, beta subunit (TCRB; 186930). Van der Burg et al. (2000) pointed to the homozygous (autosomal recessive) deletion of 290 bp in a severe case of ALPS reported by Rieux-Laucat et al. (1995) and the 3 sibs with compound heterozygosity for 2 missense point mutations (Bettinardi et al., 1997); see 134637.0006 and 134637.0007.

.0014 SQUAMOUS CELL CARCINOMA, BURN SCAR-RELATED, SOMATIC [TNFRSF6, ASN239ASP]

In a burn scar-related squamous cell carcinoma, Lee et al. (1999) detected an A-to-G transition at nucleotide 957 of the TNFRSF6 gene, resulting in an asn239-to-asp amino acid change within the FAS death domain.

.0015 SQUAMOUS CELL CARCINOMA, BURN SCAR-RELATED, SOMATIC [TNFRSF6, ASN102SER]

In a burn scar-related squamous cell carcinoma, Lee et al. (1999) detected an A-to-G transition at nucleotide 547 of the TNFRSF6 gene, resulting in an asn102-to-ser amino acid change within the FAS ligand-binding domain.

.0016 SQUAMOUS CELL CARCINOMA, BURN SCAR-RELATED, SOMATIC [TNFRSF6, CYS162ARG]

In a burn scar-related squamous cell carcinoma, Lee et al. (1999) detected a T-to-C transition at nucleotide 726 of the TNFRSF6 gene, resulting in an cys162-to-arg amino acid change within the FAS transmembrane domain.

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